Fetal Storage Disorders

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Many of the so-called inborn errors of metabolism, the storage diseases, produce inclusions or vacuoles in the tissues of affected individuals. The placenta is often similarly involved, and chorionic villus biopsy (CVS) is now more often employed to make the diagnosis prenatally, as, for instance, in diagnosing lipofuscinosis [54]. Electron microscopy and special enzyme studies are usually helpful for the precise diagnosis of the defect involved. Thus, appropriate fixation is needed when such disease is suspected, and it must also be anticipated at the time of CVS, as many of the lysosomal inclusions are highly water and lipid-solvent soluble. Since many of these diseases are the cause of fetal hydrops, the cases of nonimmune hydrops fetalis warrant special attention. An excellent ultrastructural study of 11 cases has been published by Jones et al. [34] that details procedures and findings, and Fox [21] has shown other material. These publications depict the findings in admirable detail and provide additional literature. There are many thousands of diseases but broadly they may be divided into errors of:

- Carbohydrate metabolism
- Protein metabolism
- Fatty acid oxidation
- Glycogen storage

Inborn errors of metabolism account for approximately 1% of cases of nonimmune hydrops [8] with the most important cases being summarized below (Table 24.1). The placenta may also be enlarged and hydropic. Thus, when hydrops fetalis or hydropic placenta is diagnosed and possible diagnostic issues are being raised (see Chap. 23), the need to consider inborn errors of metabolism/storage disorders is obvious, and special techniques to identify the defect are in order. Tissues may be preserved in different fixatives for possible recognition of inclusions; however, though the placenta may be hydropic in many of these inborn errors, vacuolations or inclusions are not always apparent, and further testing may not be considered leading to missed diagnoses. Therefore, a special plea is made here that the placenta of hydrops cases be scrutinized especially carefully. Historically, samples were collected for electron microscopy and/or frozen for possible future enzyme studies. Such studies still have merit but are gradually being replaced by targeted genetic testing; indeed the use of specific gene panel testing may even bypass the enzymology and the morphological view of predicting the defect based on the morphological view of predicting the defect based on site of placental vacuolation (trophoblast syn/cyto, endothelium, or stroma) may well become obsolete [68]. Clearly, many more such enzymatic errors or storage diseases will come to be recognized when appropriate studies are undertaken.

Inborn Errors of Metabolism and Placental Studies

G_{M1} gangliosidosis is an autosomal recessive (AR) lysosomal storage disease characterized by accumulation of ganglioside substrates in lysosomes. Clinically, patients show variable degrees of neurodegeneration and skeletal abnormalities, characterized by deficiency of the β-galactosidase enzyme, due to mutations in the *GLB1* gene, resulting in accumulation of glycolipids, oligosaccharides, and especially GM1 ganglioside [5, 41]. By amniocentesis at 14 weeks, Lowden et al. [45] identified the absence of β-galactosidase, which affects the degradation of GM1 ganglioside. The pregnancy was terminated; typical inclusions (zebra bodies) were ultrastructurally

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identified in the fetal ganglion cells. Although other fetal cells were unremarkable in paraffin sections, vacuoles were seen in epon-embedded material. The placenta showed numerous "empty vacuoles" in the syncytial cytoplasm, extravillous trophoblast, and Hofbauer cells [56]. They were visible even in paraffin sections. Presumably, these contain the water-soluble storage product and galactose-rich mucopolysaccharide. Fetal hydrops was detected at the 23-week gestation ultrasound, which also showed a hydropic placenta [63] (Table 24.1).

The *G_{M2} gangliosidoses* are a group of three related genetic disorders that result from a deficiency of the enzyme beta-hexosaminidase. This enzyme catalyzes the biodegra-

Table 24.1 Inborn errors of metabolism. Common names and synonyms, genes, and mode of inheritance

Disease	Synonyms	Hydrops fetalis as major feature	Placental findings [20]	Gene involved and cytogenetic location
GM1 gangliosidosis	Beta-galactosidase-1 (GLB1) deficiency	√ [45, 56, 63]	Vacuolated trophoblast	Mutations in the *GLB1* gene Cytogenetic location – 3p22.3
GM2 gangliosidosis type I	B variant GM2 gangliosidosis GM2 gangliosidosis, type 1 HexA deficiency Hexosaminidase A deficiency Hexosaminidase alpha-subunit deficiency (variant B) Sphingolipidosis, Tay-Sachs Tay-Sachs disease		Vacuolated trophoblast and Hofbauer cells, amnion Absent hexosaminidase in CVS [26]	Mutations in the *HEXA* gene Cytogenetic location – 15q23-q24
GM2 gangliosidosis type II	Beta-hexosaminidase beta-subunit deficiency GM2 gangliosidosis, type 2 GM2 gangliosidosis, type II Hexosaminidase A and B deficiency disease Sandhoff-Jatzkewitz-Pilz disease Sandhoff's disease Total hexosaminidase deficiency		Multiple parallel arrays in lysosomes of stroma, vacuolated syncytium, myelin bodies in the trophoblast and endothelium [21, 34]	Mutations in the *HEXB* gene Cytogenetic location – 5q13.3
Glycosphingolipidosis	α-Galactosidase A deficiency/absence Fabry's disease		Lamellar lysosomal inclusions in decidual cells, chorionic cells normal, in heterozygous carrier [70]	Mutations in the *GLA* gene Cytogenetic location – Xq 22.1
Mucolipidosis type I	Sialidosis Cherry-red spot myoclonus syndrome Mucolipidosis I Mucolipidosis type I Myoclonus cherry-red spot syndrome	√ [44]	Vacuolated trophoblast and stroma Hofbauer cells, normal amnion [12, 23, 42, 46, 55, 66]	Mutations in the *NEU1* gene Cytogenetic location – 6p21.33
Mucolipidosis II (I-cell disease)	I-cell disease Inclusion cell disease MLII Mucolipidosis II Mucolipidosis type II	√ [43]	Vacuolated syncytium, vacuolated Hofbauer and X-cells Occasional myelin figures in EM [14, 52, 53, 58]	Mutations in the *GNPTAB* gene Cytogenetic location – 12q23.2
Mucolipidosis type IV	Ganglioside sialidase deficiency ML4 MLIV Sialolipidosis		Vacuolated stroma Hofbauer cells with lamellar inclusions of the endothelium [54, 60]	Mutations in the *MCOLN1* gene Cytogenetic location – 19p13.2
Mucopolysaccharidosis I	Hurler-Scheie syndrome Hurler syndrome IDUA deficiency MPS I MPS I H MPS I H-S MPS I S Scheie syndrome	√ in some cases	Vacuolation of fibroblasts, Hofbauer cells, and syncytium [7, 34]	Mutations in the *IDUA* gene Cytogenetic location – 4p16.3
Mucopolysaccharidosis III	Sanfilippo's disease		Vacuolated syncytium, absent heparin-N-sulfatase [34, 37]	Mutations in the *SGSH* gene Cytogenetic location – 17q25.3 For variants see text

Table 24.1 (continued)

Disease	Synonyms		Hydrops fetalis as major feature	Placental findings [20]	Gene involved and cytogenetic location
Mucopolysaccharidosis IV	Morquio-Brailsford disease Morquio disease Morquio syndrome Morquio's disease Morquio's syndrome Mucopolysaccharidosis (MPS) IV (A, B)		√ [29]	Edema of villi, vacuolated Hofbauer cells [4]	Mutations in the *GLB1* gene Cytogenetic location – 3p22.3 Mutations in the *GALNS* gene Cytogenetic location – 16q24.3
Mucopolysaccharidosis VII	Beta-glucuronidase deficiency GUSB deficiency MPS VII MPS7 Mucopolysaccharidosis 7 Mucopolysaccharidosis VII Sly syndrome		√ [28]	Vacuolation of Hofbauer cells [18, 22, 48, 50, 72]	Mutations in the *GUSB* gene Cytogenetic location – 7q11.21
Sialic acid storage disease	Salla disease N-Acetylneuraminic acid storage disease NANA storage disease Sialuria, Finnish type			Vacuolated syncytium and Hofbauer cells with amorphous and fibrillar material, vacuolated extravillous trophoblast and amnionic epithelium [23, 32, 34, 56]	Mutations in the *SLC17A5* gene Cytogenetic location – 6q13
Galactosialidosis	Deficiency of cathepsin A Goldberg syndrome Lysosomal protective protein deficiency Neuraminidase deficiency with beta-galactosidase deficiency PPCA deficiency		√ [16]	Vacuolated syncytiotrophoblast, extravillous trophoblast, and villous Hofbauer cells. Electron microscopy revealed numerous membrane-bound electron-lucent lysosomes, mainly within the syncytiotrophoblast	Mutations in the *CTSA* gene Cytogenetic location – 20q13.12
Gaucher disease	Cerebroside lipidosis syndrome Gaucher splenomegaly Gaucher syndrome Gaucher's disease Gauchers disease GD Glucocerebrosidase deficiency Glucocerebrosidosis Glucosyl cerebroside lipidosis	Glucosylceramidase deficiency Glucosylceramide beta-glucosidase deficiency Glucosylceramide lipidosis Kerasin histiocytosis Kerasin lipoidosis Kerasin thesaurismosis Lipoid histiocytosis (kerasin type)	√ in type II [11]	Erythroblastosis fetalis with increased fetal red cells in villous vessels [11, 23, 24, 62, 64]	Mutations in the *GBA* gene Cytogenetic location 1q22
Sphingomyelin storage disorder	Niemann-Pick type A Lipid histiocytosis Neuronal cholesterol lipidosis Neuronal lipidosis NPD	Sphingomyelin lipidosis Sphingomyelin/ cholesterol lipidosis Sphingomyelinase deficiency	√ in NP type C [47, 57]	Vacuolization and laminated inclusions (myelin bodies) in syncytium, stroma, Hofbauer cells, umbilical cord, fibrocytes, hydrops [47, 58, 59, 71]	Niemann-Pick disease types A and B is caused by mutations in the *SMPD1* gene Cytogenetic location – 11p15.4
Cholesterol ester storage disease	Wolman disease Acid esterase deficiency Acid lipase deficiency Familial visceral xanthomatosis Familial xanthomatosis	LAL deficiency LIPA deficiency Primary familial xanthomatosis Primary familial xanthomatosis with adrenal calcification	√ [9, 35]	Massive lysosomal cholesterol and lipid accumulation was demonstrated in syncytiotrophoblasts and in fetal hepatocytes and adrenal cells Vacuolation of trophoblast and Hofbauer cells	Mutations in the *LIPA* gene Cytogenetic location 10q23.31
Glycogen storage disorder type II	Pompe's disease			Vacuoles full of glycogen in EM in stroma, endothelium, cytotrophoblast, lysosomes [10, 34, 56]	Mutations in the *GAA* gene Cytogenetic location: 17q25.3

CVS chorionic villus sample, *EM* electron microscopy

dation of fatty acid derivatives known as gangliosides. The diseases are better known by their individual names [15].

Tay-Sachs disease (G_{M2} gangliosidosis type I) is an autosomal recessive (AR), progressive neurodegenerative disorder which, in the classic infantile form, is usually fatal by age 2 or 3 years. It results from mutations in the *HEXA* gene which disrupts the activity of beta-hexosaminidase A, which prevents the enzyme from breaking down G_{M2} ganglioside. As a result, this substance accumulates to toxic levels, particularly in neurons in the brain and spinal cord. Progressive damage caused by the buildup of G_{M2} ganglioside leads to the destruction of these neurons, which causes the signs and symptoms of the disease. In the studies by Jones et al. [34], it was found to produce vacuolation of syncytiotrophoblast, with occasional myelin bodies in villous stromal cells.

Sandhoff's disease (G_{M2} gangliosidosis type II), also AR, is clinically indistinguishable from Tay-Sachs. It results from mutations in the *HEXB* gene; the *HEXB* gene provides instructions for making a protein subunit of two related enzymes, beta-hexosaminidase A and beta-hexosaminidase B. Each of these is composed of two subunits. Beta-hexosaminidase A includes one alpha subunit (produced from the *HEXA* gene) and one beta subunit (produced from the *HEXB* gene). Beta-hexosaminidase B is composed of two beta subunits, produced from the *HEXB* gene. Beta-hexosaminidase A and beta-hexosaminidase B are found in lysosomes and play a critical role in the brain and spinal cord (central nervous system). They break down fatty compounds, sphingolipids, complex sugars, oligosaccharides, and molecules that are linked to sugars (such as glycoproteins). Membranous arrays were occasionally identified in the lysosomes of stromal cells in a case of Sandhoff's disease, together with some myelin body formation in the trophoblast and endothelium [34].

GM2 gangliosidosis, AB variant, is included here for completeness, but there appears to be no description of placental pathology in this disorder. It is a rare autosomal recessive neurodegenerative disorder occurring due to deficiency of GM2 activator protein resulting from the mutation in *GM2A* gene. It progressively destroys nerve cells (neurons) in the brain and spinal cord.

Fabry's disease is an X-linked lysosomal storage disease which manifests as progressive renal failure, cardiac disease, cerebrovascular disease, small-fiber peripheral neuropathy, and skin lesions, among other abnormalities. It is caused by deficiency of lysosomal α-galactosidase A, resulting in the accumulation of globotriaosylceramide (ceramide trihexoside). A pregnancy in a patient with this disease was described by Popli et al. [51] after she had received a renal allograft. The placenta of the term fetus was normal, but the decidual cells contained argyrophilic granules which, electron micrographically, had the appearance similar to zebra bodies. The fetal portions of the placenta were normal. Thurberg and Politei [70] found globotriaosylceramide deposits within multiple cell types of the placenta, cord, and membranes.

Bouwman et al. [13] report the evaluation of placental tissue of two pregnancies in Fabry-affected mothers, (1) an unaffected male newborn (placenta A) and (2) an affected female newborn (placenta B). The mother of the female affected offspring was treated with recombinant alpha-galactosidase A (enzyme replacement therapy, ERT) during the pregnancy (placenta B). Storage material was only detected in smooth muscle cells of the umbilical cord of placenta B. No accumulation was seen in both placentae. Combining these results with the outcome in two earlier described placentae, a heterogeneous picture emerges. This may be due to differences in disease severity in the mothers or severity of disease in their offspring. In addition, a possible effect of ERT on placental globotriaosylceramide accumulation could also explain lack of its storage in placenta B.

Sialidosis (*mucolipidosis type I*) is an autosomal recessive disorder, caused by a mutation in the neuraminidase gene (*NEU1*), leading to a deficiency of the lysosomal enzyme α-*N*-acetyl neuraminidase which results in an accumulation of sialic containing compounds within the lysosomes. Sialidosis has been divided into two subtypes on the basis of age of onset and disease severity: type I (normomorphic or mild form, also known as cherry-red spot myoclonus) and sialidosis type II (dysmorphic or severe form) [36]. Laver et al. [42], Sergi et al. [61], and Godra et al. [25] found typical storage vacuoles in Hofbauer cells and the villous syncytium. Mahmood and Haleem [46] described vacuolation of trophoblasts, Hofbauer cells, and placenta X-cells in a stillborn fetus with sialidosis; PAS-diastase staining showed fine PAS-positive granules within the vacuolated cells. Electron microscopy showed that the cytoplasm of most of the vacuolar syncytiotrophoblast and Hofbauer cells was filled by membrane-bound vesicles which were translucent and contained fine granules, while an occasional vesicle showed incomplete myelin-like bodies. The placenta of the 20-week fetus described by Sergi et al. [61] showed generalized villous maturational delay, and the cytoplasm of the vacuolated trophoblastic cells displayed marked acid phosphatase staining. Amniocyte morphology in this disease has been reported to be normal by electron microscopic study [66]. Khan and Sergi [36] showed vacuolar degeneration of the syncytiotrophoblast in the congenital form of *type II sialidosis*.

Gillan et al. [23], who discussed congenital ascites in various storage disorders (*sialidosis, Salla disease,* G_{m1} *gangliosidosis, Gaucher's disease*), depicted a placental villus with vacuolated syncytial cytoplasm of a fetus with *Salla disease*.

Mucolipidosis type II or *I-cell disease* is a rare and fatal autosomal recessive disorder caused by mutations in the *GNPTAB* gene that prevent the production of functional GlcNAc-1-phosphotransferase which is involved in the

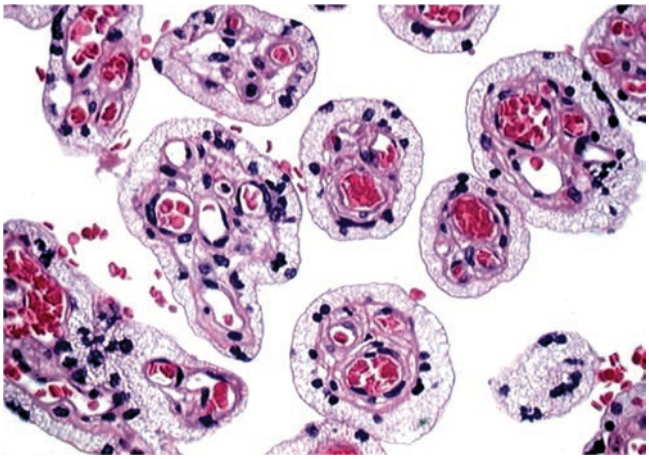

Fig. 24.1 Appearance of villi in "I-cell" disease (mucolipidosis II). The syncytium is characteristically uniformly finely vacuolated. (Courtesy of Dr. Scott Hyde, Tulsa, Oklahoma)

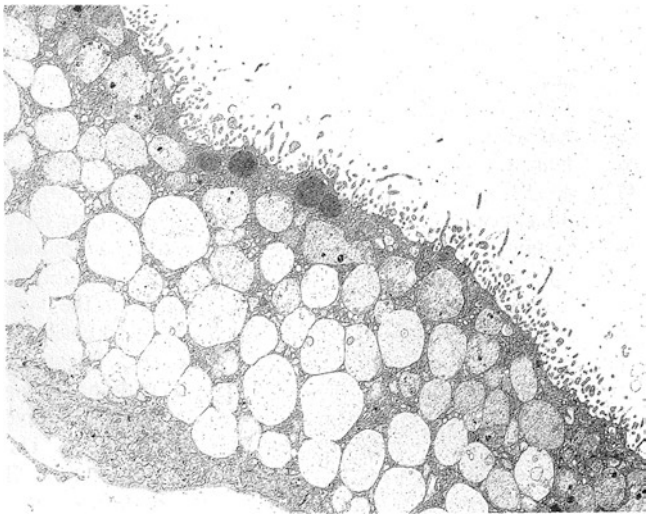

Fig. 24.2 Syncytium in case of I-cell disease. Note extensive fine vacuolation, the storage site of washed-out glycolipids in the syncytial cytoplasm (EM × 6700). (Courtesy of Dr. Juhani Rapola, Helsinki, Finland)

process of attaching a molecule called mannose-6-phosphate to specific digestive enzymes to allow entry to lysosomes, allowing larger molecules to accumulate. Placental involvement with inclusion-bearing cells was first demonstrated in a case report of Powell et al. [52]. The syncytium and Hofbauer cells were primarily affected; the vacuoles of formerly mucolipid-containing lysosomes were readily apparent in paraffin sections of the placenta (Fig. 24.1), but the features were much enhanced by processing the tissues in epoxy resin. The authors of this paper emphasized that only fetal cells contained the vacuoles. Affected tissue included the "X-cells" of cell columns and the placental floor. There were no inclusions in decidual cells, and they used this to further identify X-cells as being of fetal origin. The placenta was grossly pale and somewhat enlarged; the fetus was not hydropic. The same report contained three additional and similar storage diseases that affected the placenta, but the precise nature of their storage disorders could not be identified. Abe et al. [1] and Nagashima et al. [49] have described other morphological studies. Several investigators have further elaborated on placental aspects of mucolipidosis type II. Thus, Rapola and Aula [53] beautifully demonstrated the ultrastructural changes of the syncytium and suggested that the diagnosis could easily be made from this material alone (Fig. 24.2). With chorionic villus biopsy, this would now be possible without having to resort to enzymatic study. Hug et al. [30] have shown that maternal serum hexosaminidase levels are increased in pregnancies affected by I-cell disease which allows diagnosis without uterine invasion. Chapel and his colleagues presented a case of mucolipidosis II that affected one of dichorionic-diamnionic twin pregnancy delivered at 36-week gestation. The affected placenta displayed marked vacuolization of the syncytiotrophoblast and Hofbauer cells, which was confirmed on ultrastructural examination [14]. Baldo et al. [7] found alterations related to MPS storage, although not pronounced, may be observed in placental tissue of patients affected by MPS II and MPS VI.

Mucolipidosis III alpha/beta is a milder disorder which is caused by mutations in the *GNPTAB* gene. Instead of preventing the production of any enzyme, these mutations reduce the activity of GlcNAc-1-phosphotransferase. Mucolipidosis III alpha/beta and mucolipidosis II alpha/beta represent two ends of a spectrum of disease severity.

Mucolipidosis IV is an autosomal recessive disease characterized by severe neurologic and ophthalmologic abnormalities, due to mutations in the *MCOLN1* gene which encodes a protein called mucolipin-1. The *MCOLN1* gene provides instructions for making a protein called mucolipin-1, located in membranes of lysosomes and endosomes; though its role is not completely understood, it plays transport of lipids and proteins between these two compartments. This disease has been diagnosed from cultured amnionic fluid cells by Kohn et al. [38]. The amnion cells contained multiple single-membrane bounded inclusions. Mesodermal elements, however, were negative. Although it may appear superficially that this disease is similar to I-cell disease, in this condition, the amnion, not syncytium and Hofbauer cell, has the vacuolation [20].

Morquio's disease (mucopolysaccharidosis (MPS) type IVA), which may present with short stature, skeletal dysplasia, dental anomalies, and corneal clouding, is caused by mutations in the *GALNS* gene which encodes N-acetylgalactosamine-6-sulfatase, a lysosomal exohydrolase required for the degradation of the glycosaminoglycans, keratan sulfate, and chondroitin 6-sulfate. Mutations in the *GLB1* gene which encodes β-galactosidase disrupt the breakdown of keratan sulfate leading to MPS IVB. In general, the two types of MPS IV cannot be distinguished

by their signs and symptoms. Type IVA has been diagnosed from enzyme analysis of chorionic villus biopsy [4].

Within the family reported by Applegarth et al., nonimmune hydrops fetalis had occurred in previous pregnancies. The authors drew attention to previous reports of hydrops with *Gaucher's, Wolman, and Salla diseases, with sialidosis and mucopolysaccharidosis type VII*. In their family, they had a hydropic fetus with a bulky placenta. Vacuolar villous edema and prominent Hofbauer cells were found, but there was no histological evidence of storage products in the trophoblast.

MPS IIIA (Sanfilippo) is characterized by severe central nervous system degeneration, but only mild somatic disease. Onset of clinical features usually occurs between 2 and 6 years; severe neurologic degeneration occurs in most patients between 6 and 10 years of age, and death occurs typically during the second or third decade of life. It is caused by mutations in the *SGSH* gene. *MPS IIIB* is caused by mutations in the *NAGLU gene*. Mutations in the *HGSNAT* gene result in *MPS IIIC*, and *GNS* gene mutations cause *MPS IIID*. Mutations in these genes reduce or eliminate enzyme function which disrupts the breakdown of heparan sulfate. As a result, partially broken down heparan sulfate accumulates within cells, specifically inside the lysosomes.

Sly disease (MPS VII) is an autosomal recessive disease characterized by hepatomegaly, skeletal anomalies, coarse facies, and variable degrees of mental impairment results from mutations in the *GUSB* gene which encodes beta-glucuronidase (β-glucuronidase), an enzyme involved in the breakdown of large sugar molecules called glycosaminoglycans. Fetal hydrops and vacuolation of the placental Hofbauer cells have been described by several authors [18, 22, 48, 50, 72] (Fig. 24.3).

Sialic acid storage diseases are autosomal recessive neurodegenerative disorders that may present as a severe infantile form (infantile sialic storage disorder, ISSD) or as a slowly progressive adult form that is prevalent in Finland (*Salla* disease). The main symptoms are hypotonia, cerebellar ataxia, and mental retardation; visceromegaly and coarse features are also present in the infantile cases. It results from mutations in the *SLC17A5* gene which reduce or eliminate sialin activity result in a buildup of free sialic acid in the lysosome. Jones et al. [34] identified the Hofbauer cells, endothelium, and syncytium to be packed with clear, membrane-bound vacuoles [32] (Fig. 24.4). Roberts et al. [56] also found vacuolation in extravillous trophoblast and amnionic epithelium.

Galactosialidosis is a rare autosomal recessive lysosomal storage disease caused by mutations in the *CTSA* gene, which encodes the protective protein cathepsin A. The loss of function of this protein causes a secondary deficiency of beta-galactosidase and N-acetyl-a-neuraminidase enzymes activities [2]. Kostadinov et al. [40] reported a case of unsuspected fetal galactosialidosis presenting as severe intrauterine growth restriction and oligohydramnios prenatally and as hyperinsulinemic hypoglycemia in the immediate postnatal period. Placental pathology examination showed striking vacuolations of the villous syncytiotrophoblast, extravillous trophoblast, and villous Hofbauer cells. Electron microscopy revealed numerous membrane-bound electron-lucent lysosomes, mainly within the syncytiotrophoblast.

Gaucher's disease may cause fetal hydrops. Gaucher's disease is an autosomal recessive lysosomal storage disorder caused by mutations in the *GBA* gene, resulting in deficiency in the enzyme glucocerebrosidase (also called glucosylceramidase or acid β-glucosidase), which hydrolyzes glucosylceramide into ceramide and glucose [67]. The disease

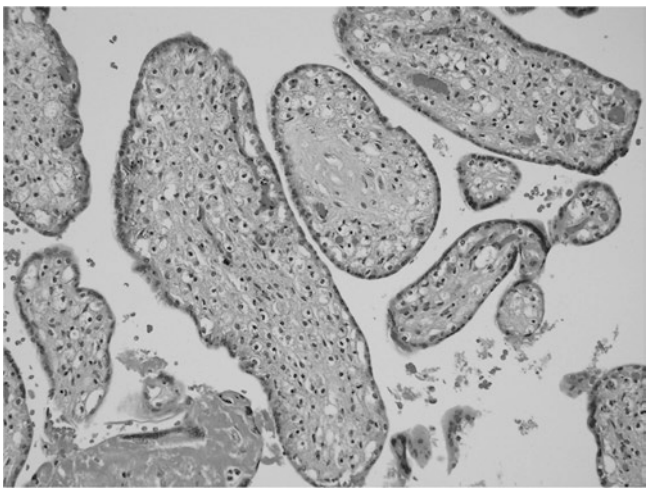

Fig. 24.3 Vacuolation of the placental Hofbauer cells in a case of mucopolysaccharidosis (MPS) VII

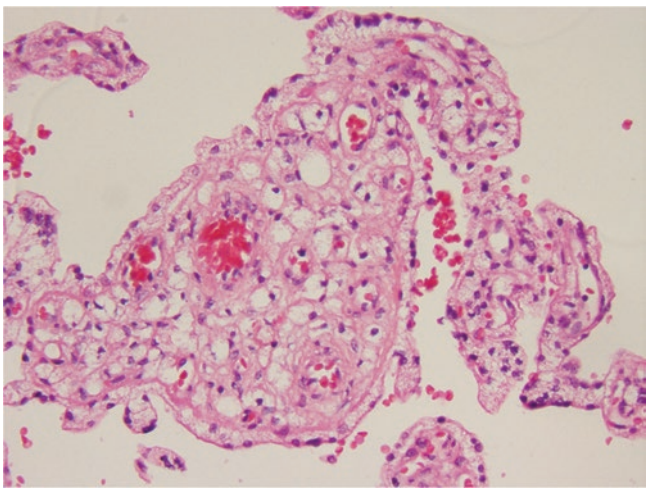

Fig. 24.4 Sialic acid storage disease: the Hofbauer cells, endothelium, and syncytium are packed with clear, membrane-bound vacuoles

phenotype is variable: type I (non-neuronopathic), characterized by no neurological manifestations, which is the commonest; type II (acute neuronopathic); and type III (subacute neuronopathic) which are characterized by neurological impairment [67].

In the case described by Ginsburg and Groll [24], polyhydramnios complicated the second pregnancy of a patient in the second trimester. At 34 weeks, she delivered a macerated, hydropic fetus. The large and edematous placenta had the macroscopic features of erythroblastosis fetalis. Soma et al. [64] illustrated a characteristic case with recurrent hydrops fetalis in a Japanese pedigree. They included EM pictures and again features of erythroblastosis fetalis with numerous nucleated red blood cells present in villous capillaries. Placental examination from a 28-week hydropic pregnancy showed placentomegaly with villous hydrops, fetal erythroblastosis, and infiltration of villous stroma by mono- and multinuclear histiocytic cells containing ample cytoplasm with delicate fibrillary appearance characteristic of Gaucher cells (Fig. 24.5). The cells were CD68 positive on immunohistochemistry, and the intracytoplasmic material was PAS-D and Luxol fast blue positive [11].

Niemann-Pick disease types A and B is a progressive disease associated with hepatosplenomegaly and psychomotor regression. Children with type A may also develop interstitial lung disease leading eventually to respiratory failure, and such affected children generally do not survive beyond childhood. All cases present with a cherry-red spot. Types A and B are caused by mutations in the *SMPD1* gene, leading to acid sphingomyelinase deficiency which can be diagnosed from absent enzyme activity in amnionic fluid. Unusual echogenic densities in the placentas of several cases were sonographically demonstrated by Schoenfeld et al. [59] that also had thick chorionic plates. Vacuolated syncytium, Hofbauer cells, and fibrocytes of the umbilical cords contained accumulations of sphingomyelin, as did the chorion laeve.

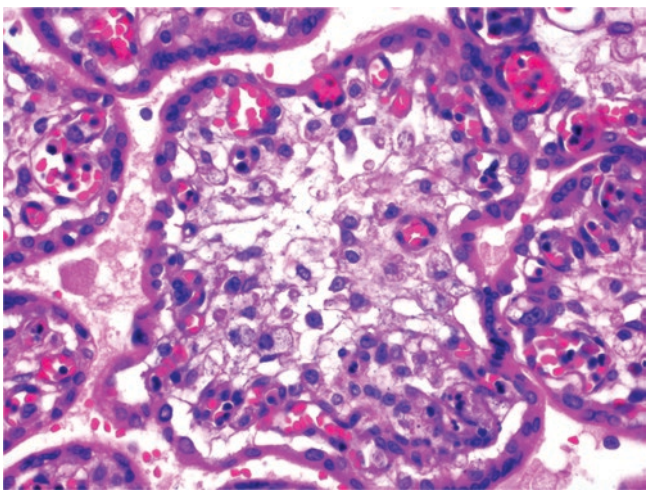

Fig. 24.5 Infiltration of villous stroma by characteristic Gaucher cells. (Courtesy of Dr. Admire Matsika, Brisbane, Australia)

Niemann-Pick disease type C is a rare inherited autosomal recessive neurodegenerative disease that affects infants, children, and adults. It is caused by an accumulation of lipids (fats) in the liver, brain, and spleen. NP-C is divided into two subtypes, NP-C1 and NP-C2, as each is caused by a different gene mutation. Approximately 95 percent of NP-C cases are caused by genetic mutations in the *NPC1* gene, with the other 5 percent caused by mutations in the *NPC2* gene. It does not result in visible storage products of the placenta; however, when tissue is obtained from CVS and cultured under special conditions, the tissue-cultured cells of affected fetuses have been shown to accumulate laminated inclusions of nonesterified cholesterol (myelin bodies) which can then be stained with filipin for unesterified cholesterol, and the diagnosis may thus be secured [27, 34, 71].

Cholesterol ester storage disease and *Wolman disease* are both caused by mutations in the *LIPA* leading to deficiency of lysosomal acid lipase. The two diseases appear to vary in the degree of residual enzyme activity [3]. Wolman presents as an early-onset fulminant disorder of infancy with massive infiltration of the liver, spleen, and other organs by macrophages filled with cholesteryl esters and triglycerides. Death occurs early in life. Cholesterol ester storage disease may present later and in a milder form. Desai et al. [19] found lysosomal lipid deposits in *cholesterol ester storage disease* with massive lysosomal cholesterol and lipid accumulation demonstrated in fetal hepatocytes, adrenal cells, and syncytiotrophoblasts.

Pompe's disease (glycogen storage disease type II; α-1,4-glucosidase deficiency) is an autosomal recessive, lysosomal storage disease characterized by a mutation of the acid α-glucosidase (*GAA*) gene. Reduced activity of α-glucosidase (also known as acid maltase) allows complex sugars to build to toxic levels. In routine examination of the placenta, the unusual finding is the cytoplasmic vacuolation of amnionic connective tissue cells and the villous capillary endothelial cells [10, 56]. Electron microscopy, however, showed typical membrane-bounded, glycogen-filled inclusions in capillary endothelial cells and in the villous stroma. They were present even in midtrimester abortuses. Hug et al. [31] described the diagnosis from CVS at 10 weeks. The previous pregnancy had resulted in an affected child. Electron microscopic examination 5 days after biopsy identified the typical glycogen-packed membrane-enclosed inclusions in many fetal cells, including fibrocytes that appear as vacuoles in histologic study. These authors insisted that the demonstration of vacuoles alone is insufficient for the diagnosis. Jones and her collaborators [34] made similar findings of lysosomal glycogen accumulation. These were seen in the cytotrophoblast, endothelium, fibrocytes, and pericytes. Konstantinidou et al. [39] reported in an abstract abnormal

glycogen deposits primarily located in extravillous trophoblast; they were PAS positive but diastase resistant in two unrelated people.

Closing Comment

It is apparent from these descriptions that many congenital enzyme deficiencies can be diagnosed from amnionic fluid cultures and chorionic villus samples and that they may be accompanied by placental manifestations. The location and type of inclusion cannot always be anticipated. Cozzutto [17] reported on a macerated stillborn whose placenta had extensive vacuolar changes and interpreted the vacuolated "stromal decidual cells," which he did not depict, as "convincingly demonstrating" that the foam cells are a transformation secondary to edema or fetal death. Fetal death or edema does not give rise to vacuolation, and the abundance of foam cells, the disposition of trophoblastic vacuoles, and irregular calcifications observed by him are indicative of an unidentified fetal storage disorder. But then, calcifications have been seen in Gaucher's disease [65], highlighting the complexity of enzyme disorders. Some of the cellular glycolipids are highly water soluble, and therefore the empty appearance of the vacuoles is the usual finding in many fetal storage disorders. Chorionic villus biopsy has become of great value in selected cases, especially for prenatal counseling. In this area of research, some published animal models closely parallel the human disease. Most known animal "models" of storage disease and spontaneous occurrences of inborn errors of metabolism were reviewed by Jolly and Walkley [33]. Their use may be of value, particularly in attempts at therapy, but also for the study of their placentas [6]. A more recent review by Sun [69] highlighted the main clinical features, diagnosis, and management of lysosomal storage disorders with an emphasis on those for which treatment is available. Over the next few years, inborn errors of metabolism are likely to be diagnosed using molecular genetics and targeted panels, but this should not deter those involved in examining the placenta from being closely involved in such diagnoses when such diseases are suspected from histological examination. Knowledge of the placental changes may lead to more specific analysis. Knowledge of the specific variant involved in a family enables early antenatal diagnostic testing in future pregnancy.

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